

## Recurrent Esophageal Carcinoma After Esophagectomy With Three-Field Lymph Node Dissection

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To evaluate the effect of the extended lymphadenectomy for thoracic esophageal carcinoma, the pattern of recurrence in the 50 patients with pT3 tumors who underwent esophagectomy with cervical, mediastinal, and abdominal lymph node dissection (3-F) (group A) was compared with that of 100 patients at pT3 who underwent esophagectomy without upper mediastinal and cervical lymphadenectomy (2-F) (group B). The cumulative 5-year survival rate for 115 patients who underwent 3-F was 50.9%. Cumulative 5-year survival rates for patients in groups A and B were 36.8% and 22.0%, respectively. The survival curve for group A was significantly better than group B ( $P = 0.02332$ ). Lymphatic recurrence was noted less frequently in group A (8/23) than in group B (31/49) ( $\chi^2 = 5.1149$ ), whereas the rate of hematogenous recurrence was similar. Extension of the field of lymph node dissection reduced the lymph node recurrence in patients with thoracic esophageal carcinoma, which may have positively affected patient survival. © 1996 Wiley-Liss, Inc.

**KEY WORDS:** esophagus, lymphadenectomy, recurrence, survival rate

### INTRODUCTION

Many surgeons and oncologists deny the survival benefit of lymph node dissection for patients with esophageal carcinoma, because they regard the disease with metastasis in the lymph nodes as systemic rather than localized. Certainly, a leading cause of death in these patients is recurrent disease, although recent reports have shown a marked improvement in patient survival after radical esophagectomy with extended lymph node dissection [1-3].

Until the mid-1980s, the standard transthoracic esophagectomy procedure used in our institute consisted of esophagectomy with dissection of the middle and lower mediastinal and abdominal pericardiac lymph nodes, which is today called two-field lymph node dissection (2-FLND). In that operation, the upper mediastinal lymph nodes were left behind, except those around the azygos vein. Beginning in 1982, the field of lymph node dissection was gradually extended to the upper mediastinum

and in 1985, to the neck, a procedure known as three-field lymph node dissection (3-FLND). This method has since become a standard surgical procedure in our institute [3].

Although some reports do analyze patterns of recurrence after esophagectomy with 2-FLND or the data of autopsy studies in patients with esophageal carcinoma [4,5], changes in the patterns of recurrence after extended lymph node dissection have never been documented. As patient survival in our institute evidently improved after introduction of 3-FLND [3], there may be some alterations in pattern of recurrence. To clarify the effect of extension of lymph node dissection on tumor recurrence,

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**TABLE 1. Clinicopathologic Factors and Recurrent Disease of Patients Who Underwent Esophagectomy With 3-Field Dissection**

Factors	No. patients with recurrence	
	Positive/Negative/Unknown	Total
Tumor location <sup>a</sup>		
Upper thoracic	3/5/0	8
Midthoracic	19/38/3	60
Lower thoracic	11/36/0	47
Clinical depth of tumor invasion <sup>a</sup>		
Tis-T2	12/53/2	67
T3	18/20/1	39
T4	3/6/0	9
Pathologic classification <sup>b</sup>		
Squamous cell carcinoma	31/70/3	104
Adenosquamous carcinoma	0/2/0	2
Undifferentiated carcinoma	0/2/0	2
Carcinosarcoma	1/4/0	5
Adenocarcinoma	0/0/0	0
Others	1/1/0	2
Pathological depth of tumor invasion <sup>a</sup>		
pTis	0/3/0	3
pT1	2/33/0	35
pT2	7/14/1	22
pT3	23/25/2	50
pT4	1/4/0	5
Pathological lymph node metastasis <sup>a</sup>		
pN1	32/38/2	72
pN0	1/41/1	43
Total patients	33/79/3	115

<sup>a</sup>1987 TNM classification [7].<sup>b</sup>WHO classification [11].

change of recurrence patterns after introduction of 3-FLND for esophagectomy were analyzed.

## MATERIALS AND METHODS

As the progression of esophageal carcinoma is generally rapid, most recurrences appear within 3 years after surgery, and published reports have usually shown horizontal survival curves after 3 years [1,6]. To evaluate the effect of extended lymph node dissection, the pattern of recurrence in patients with thoracic esophageal carcinoma who underwent 3-FLND >3 years previously was investigated.

From January 1986 through December, 1991, 115 patients with thoracic esophageal carcinoma underwent esophagectomy and 3-FLND without residual tumor (R0 according to R classification of the TNM classification [7]). There were 103 men and 12 women with mean age of  $62.7 \pm 8.8$  (Standard Deviation, SD) years. The clinicopathologic factors and subsequent detection of recurrent disease are shown in Table I. During the decade before that period, 163 patients with thoracic esophageal carcinoma underwent R0 esophagectomy with 2-FLND in our institute.

The indications for the 2-FLND and 3-FLND were the same. Abdominal procedures and techniques of esopha-

geal reconstruction were almost similar in the two surgical procedures. The cervical and upper mediastinal lymph nodes, e.g., right paratracheal lymph nodes and lymph nodes along the right and left recurrent laryngeal nerves, were not dissected in the 2-FLND. The 3-FLND was carried out by a right thoracotomy, a median laparotomy, and a cervical collar incision. Through the right thoracotomy incision, the esophagus and periesophageal nodes, the lymph nodes along the right and left recurrent laryngeal nerves, paratracheal nodes, subcarinal nodes, and infraaortic arch nodes were dissected along with the surrounding connective tissue. Via laparotomy, the pericardiac and celiac nodes were dissected along with the gastric cardia, with formation of a tubed stomach for esophageal substitution. The right and left cervical periesophageal nodes, the lower third of the jugular nodes, and the supraclavicular nodes were dissected through the cervical collar incision, followed by an esophagogastric anastomosis in the neck through the retrosternal route [3,8].

Recurrent carcinomas were found at follow-up examination of the patients in our outpatient clinic, except for a few that were discovered at other institutions where follow-up examinations after surgery were conducted. Not only monthly physical examinations but also semi-annual blood chemistry examinations and annual chest

**TABLE II. Background Factors of Patients With pT3 Esophageal Carcinoma Who Underwent 3-Field Dissection (Group A) and 2-Field Dissection (Group B)**

Factors	Group A (n = 50)	Group B (n = 100)	P value
	No. patients		
Sex			NS <sup>c</sup>
Men	46	91	
Women	4	9	
Clinical depth of tumor invasion <sup>a</sup>			NS
T2	8	9	
T3	38	83	
T4	4	8	
Histological classification <sup>b</sup>			NS
Squamous cell carcinoma	49	92	
Carcinosarcoma	1	2	
Undifferentiated carcinoma	0	4	
Adenosquamous carcinoma	0	1	
Others	0	1	
	Average value		
Age	61.3 yr	61.6 yr	0.4319
No. dissected lymph nodes	79	24	<0.0000001
Pathologic tumor size	5.8 cm	5.2 cm	0.0818

<sup>a</sup>1987 TNM classification at surgery [7].

<sup>b</sup>World Health Organization [11].

<sup>c</sup>NS = not significant.

X-ray, ultrasonography, CT scanning, and endoscopy were performed as routine follow-up examinations in our clinic. A final investigation of recurrent disease and patient survival was carried out in December 1994.

### Patients With pT3 Disease

To unify the tumor stage at esophagectomy, patterns of recurrence in patients with pT3 disease were compared between those who underwent 3-FLND (group A; 50 patients) and those who underwent 2-FLND (group B; 100 patients).

Background factors for the two groups of patients are summarized in Table II. Pathologic examination of the resected lymph nodes revealed that 24 patients (48%) in group A had metastasis in the cervical or upper mediastinal lymph nodes, most of which were considered to have been undissected in group B. Among the 50 group A patients, seven were given adjuvant radiotherapy and another 15 had adjuvant chemotherapy with cisplatin and vindesine. Of the 100 group B patients, 36 had postoperative irradiation and another 39 received chemotherapy with tegafur or bleomycin after surgery. These adjuvant treatments were performed on the basis of multi-institutional randomized controlled trials of adjuvant treatments.

### Statistics and Classifications

Differences between the two groups were analyzed statistically by the Chi-square test and Student's *t*-test.

The cumulative survival rates were computed by the life-table method of Cutler and Ederar [9]. Differences between adjusted survival rates were analyzed by the generalized Wilcoxon test [10]. The TNM classification (4th ed.) [7] was used to classify the tumor stage, and the WHO classification (2nd ed.) [11] was used for histological classification.

### RESULTS

The cumulative 3- and 5-year survival rates for 115 patients who underwent 3-FLND were 61.7% and 50.9%, respectively. Among them, tumor recurrence was found in 33 patients (28.7%). The majority of the patients had squamous cell carcinoma, and tumor recurrence after 3-FLND was seen in 30.7%.

Among 33 patients who were found to have recurrent disease, 13 had the first recurrence in the lymph nodes. They represented 39.4% of those patients with recurrent disease. Fifteen patients (45.5% of 33 patients) had hematogenous metastasis to the liver, lung, bone, brain, and other organs. Seven patients (21.2%) had recurrence in the wall of organs adjacent to the tumor, such as the aorta, trachea, and bronchus. Anastomotic recurrence occurred in one patient (3.0%) and pleural dissemination in one (3.0%). Among those patients, four had both hematogenic and lymphogenic recurrence, and one was found to have recurrence simultaneously in the tumor adjacent organ and in the anastomotic site. In two patients, recurrent disease was found >3 years after esophagectomy with 3-FLND. One of them was at pT1 and the other at pT2.

Among the 115 patients who underwent 3-FLND, 43 (37.4%) had no lymph node metastasis in the surgical specimens histologically (pN0), of whom 2/43 (4.7%) developed recurrent disease. One had recurrence in the neck lymph nodes, and the other died of recurrent disease in another hospital, but the site of the recurrence was unknown. Among the 72 patients at pN1, 37 (51.4%) are disease-free, 15 (20.8%) had hematogenous recurrence, 12 (16.7%) had recurrence in the lymph nodes, and 4 (5.6%) had both. The proportion of patients developing recurrence in patients at pN0 was significantly smaller than in patients at pN1 ( $P < 0.001$ ).

### Patients With pT3 Disease

Thirty-nine patients were clinically diagnosed to be at stage T3 before esophagectomy with 3-FLND, among whom 18 (47.4%) had recurrent disease. Esophagectomy with 3-FLND was generally not indicated for patients with T4 tumor. However, five tumors at pT4 could be dissected completely combined with the invaded adjacent lung or pericardium, and the patients underwent 3-FLND. The remaining 34 tumors were at pT3.

After censoring deaths due to operative complications on the day it occurred, the cumulative 3- and 5-year survival rates for group A patients were 48.0% and

**TABLE III. Recurrent Esophageal Carcinomas in Patients With pT3 Tumors Who Underwent 3-Field Dissection (Group A) or 2-Field Dissection (Group B)**

Sites of recurrence	No. patients	
	Group A (n = 50)	Group B (n = 100)
Lymph nodes*	8	31
Cervical	5	19
Mediastinal	1	10
Abdominal	3	3
Adjacent organs	7	5
Liver	4	4
Esophageal stump	1	1
Lung	1	1
Pleura	1	2
Bone	1	5
Brain	0	2
Others	2	1
Recurrence positive/ negative/uncertain (recurrence rate)	23/25/2 (47.9%)	49/44/7 (52.7%)

\* $P = 0.04632$ .

36.8%, respectively, and those for group B patients were 25.0% and 22.0%, respectively. The survival curve for group A was significantly better than that for group B ( $P = 0.02332$ ).

Mean  $\pm$ SD intervals from surgery to recurrence were  $332 \pm 224$  days for group A and  $411 \pm 498$  days for group B. Postoperative mean survival times for patients with recurrent disease in groups A and B were  $678 \pm 561$  days and  $618 \pm 580$  days, respectively. The interval from surgery to recurrence and median survival times did not differ between the two groups ( $P = 0.1844, 0.3397$ ).

Twelve patients (24%) in group A were at stage pN0, among whom only one died of unknown disease. The cumulative 5-year survival rate for these patients was 83.3% after censoring deaths due to operative complications on the day it occurred. There were 21 patients (21%) in group B at stage pN0, of whom four died of recurrent disease. In two of them, the recurrence was found in the lymph nodes, one in the bone, one in an adjacent organ, and one in pleural effusion. The cumulative 5-year survival rate was 55.4% after censoring deaths due to operative complications on the day it occurred. The difference between the recurrence rates of the two groups of patients at stage pN0 was statistically significant ( $P = 0.02641$ ). Although the survival rate for patients at stage pN0 in group A (83.3%) appeared to be better than that in group B (55.4%), the difference was not statistically significant ( $P = 0.1471$ ), which might be a result of the small numbers of patients in both groups.

The sites of recurrence first noticed in both groups are shown in Table III. After excluding those patients who died of operative complications and those in whom the site of recurrence was uncertain, the recurrent tumor was

found in 23/47 (51.1%) of group A and in 49/82 (59.8%) of group B. Among 23 group A patients with recurrent disease, 8 (34.8%) had recurrence in the lymph nodes, whereas in group B, 31/49 (63.3%) had recurrence in the lymph nodes. Lymph node recurrence among those patients with recurrent disease was significantly less in group A than in group B ( $\chi^2 = 5.1149$ ). Only one patient in group A was found to have recurrence in the mediastinal lymph nodes, compared with 10 in group B. Nineteen group B patients (38.8% of 49 patients with recurrence) had recurrent disease in the cervical lymph nodes, whereas 5/24 (20.8%) had it at this site in group A, one of whom underwent excision of the recurrent tumor in the neck 1 year after esophagectomy and lived 6 years after the resection. However, differences of the two groups with respect to the prevalence of recurrence in mediastinal and cervical lymph nodes were not significant ( $\chi^2 = 2.0018$  and  $1.3496$ ).

Among 31 group B patients with lymphatic recurrence, 11 underwent radiotherapy for the recurrent tumor, five chemotherapy, and two both. Five patients underwent excision of the recurrent tumor with radiotherapy and/or chemotherapy. All of these patients died of cancer after all. Median survival after treatment for recurrent tumor in the lymph nodes was 9.5 months (1–38 months).

Recurrent tumors in distant organs such as the liver, lung, bone, brain, and kidney are believed to originate through hematogenous metastasis. Hematogenous recurrence was found first in eight patients in group A and 13 in group B. The difference was not statistically significant ( $\chi^2 = 0.3025$ ).

## DISCUSSION

The cumulative survival rate for patients who underwent 3-FLND in our series was undoubtedly better than that reported after esophagectomy without extended lymph node dissection [12]. Recurrent disease, however, did occur in 28% of patients who underwent 3-FLND in our series, and all have since died of the disease. Recurrence is still the largest cause of death after esophagectomy for patients with thoracic esophageal carcinoma.

Esophageal carcinoma most often recurred in the lymph nodes. Sugimachi reported that of 90 patients who underwent curative esophagectomy with 2-FLND, 17 (56.7% of 30 patients with recurrence) had recurrence in the lymph nodes [4]. In our series of 115 patients who underwent 3-FLND, recurrence was found first in the lymph nodes in 13 (39.4% of patients with recurrence), an obviously smaller proportion than in Sugimachi's series. Thus it can be surmised that 3-FLND has reduced the rate of recurrence in lymph nodes.

Among the patients who underwent 3-FLND, 37% had no lymph node metastasis in the resected specimen (pN0), and of those, only 5% had subsequent recurrence. There-

fore, when a patient is found to have no positive node among those dissected by 3-FLND, it is likely that the risk of metastasis from the tumor may be small. Even in the 72 patients at stage pN1, hematogenous recurrence was seen in only 20%, and 37 have had no recurrence after 3-FLND. At least in these 37 patients, their carcinomas are considered not to have been a systemic disease but a localized one, although they did have lymph node metastases.

### 3-Field Dissection vs. 2-Field Dissection

Even after making the tumor stage uniform to stage pT3, the proportion of patients at stage pN0 in group B was smaller than in group A. That may be a reflection of the fact that there were some patients in group B who had had positive nodes only in the neck or upper mediastinum at surgery.

Although the diagnostic accuracy of tumor stage depends largely on the technique of diagnosis and the extent of the surgical procedure, pathological depth of tumor invasion is considered to be an objective tumor stage, irrespective of institutional or individual differences in diagnostic and surgical techniques. Meanwhile, patients with pT3 disease comprised the largest cohort not only in our series but also in other reported series of esophageal carcinoma [1,2,13,14].

The postoperative survival rate for patients with pT3 disease was favorable when they underwent 3-FLND, whereas that in group B was similar to the rates reported in the world literature [12]. After making background factors uniform and censoring deaths due to operative complications, the survival of patients who underwent 3-FLND was significantly better than that of patients who underwent 2-FLND. The trial of the adjuvant treatments has shown that these treatments had no significant effect on the survival of the patients [15]. Although the difference in the recurrence rates between the two groups was not statistically significant, the rate was 5% smaller in group A. The survival rate for patients with tumor recurrence in group A was also a little better, although not significantly so. Those factors together may have affected favorably the survival in group A.

Although the rates of recurrence due to hematogenous metastasis in both groups were similar, the rate of recurrence in the lymph nodes was significantly reduced in group A. The population of patients at stage pN0 in group B was significantly larger than in group A, and the rate of recurrence in patients at stage pN0 was significantly higher in group B. This suggests that some patients at stage pN0 in group B may have had undissected positive nodes in the upper mediastinum or neck, which later came to light as recurrence. In group A, nearly half of the patients were positive for metastasis in the cervical or upper mediastinal lymph nodes, most of which might have been left behind when they underwent 2-FLND

instead of 3-FLND. No patient with recurrence in the lymph nodes in group B survived the disease, irrespective of any treatment modality. By removing the positive nodes in the neck or upper mediastinum during the first operation, some patients in group A may have been saved from recurrence in the lymph nodes.

### CONCLUSIONS

Esophagectomy with three-field lymph node dissection suppressed lymph node recurrence of thoracic esophageal carcinoma, which may have contributed to improved survival of the patients.

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### COMMENTARY

Although there have been proponents of very aggressive resection with extensive lymphadenectomies in at-